Immunosuppression in hematological cancer patients with Covid-19 —Uncomplicated infections but delayed viral clearance?

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Immunosuppression in hematological cancer patients with Covid-19 – uncomplicated infections but delayed viral clearance?

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1. Introduction

A higher complication rate of Covid-19 infections in hematological malignancies, as a result of compromised immune responses associated with disease or therapy has been suggested. [1] Indeed, from the outset of the pandemic, and prior to the publication of these data [1], changes to drug schedules and life-style, to reduce risk have been recommended by disease-expert groups (https://b-s-h.org.uk/about-us/news/covid-19-updates). While several factors including the potential for contracting or transmitting infection during hospital visits and challenges in delivery of care have influenced these recommendations, a significant driver for change has been the perceived level of immunosuppression in patients with hematological cancers. The scientific rationale for these recommendations is sound, but emerging data indicate that the frequency of Covid-19 complications in patients on immunosuppression for autoimmune disorders is not different from the baseline population.[2,3] Recent reports on cancer patients including hematological malignancies too suggest that anti-cancer therapies are unlikely to worsen Covid-19 infections. [4,5].

The urgency of data reporting has however resulted in these reports lacking treatment details, [5] and with limited follow-up, little is known about the consequences of further therapy, particularly relevant to patients with acute leukemia. Here, we present information on 4 patients diagnosed with Covid-19 infection, all of whom remained relatively asymptomatic despite significant immunocompromise. We also report longitudinal changes in Covid-19 PCR cycle threshold (Ct) values in two patients who subsequently received additional cycles of chemotherapy despite persistently testing ‘positive’.

2. Methods

2.1 Patients

Data on 4 patients with Covid-19 infection were reviewed. Part of the dataset was submitted to the UK Coronavirus Cancer Monitoring Project. [5] Two outpatients presented with low-grade fever and two (Patients 3 and 4) tested 'positive' during in-patient screening. All patients were in complete remission prior to Covid-19 detection from combined nasal and pharyngeal swabs.

2.2 Laboratory detection of Covid-19

Following nucleic acid extraction, a one-step reverse transcription PCR assay (RT-PCR) targeting the RNA-dependent RNA polymerase (RdRP) gene was carried out using an ABI7500. Testing with the Allplex™ 2019-nCoV Assay (Seegene, SouthKorea®) was subsequently introduced. This assay targets N-(viral nucleocapsid protein) gene, RdRP gene and E-gene (viral envelope) and was carried out using the automated Seegene STARlet system®. Samples with a Ct value ≥35 were reported as 'detected at low level' and a value of ≥40 was arbitrarily assigned as being 'negative'.

Since hospital infection and control policies required patients to test PCR 'negative' on two consecutive swab specimens before re-admission to 'non-Covid' units, we were able to obtain serial Ct values for RdRP using the ABI7500 or Allplex™ 2019-nCoV assays in patients 3 and 4. Since Ct values for Covid-19 have been suggested to be an inverse surrogate for viral load, we related Ct values to changes in the blood neutrophil, lymphocyte and monocyte count, on or within 3 days of swabbing patients.

3. Results

3.1 Patient demographics, treatment and outcomes

A summary of the patients' hematological diagnosis, anti-cancer therapies and Covid-19 infection is presented in Table 1. Patients 1 and 2 were discharged from hospital after overnight observation and the in-patients were transferred to a Covid Unit for continued monitoring. Marrow recovery was not delayed in either patient. To maintain optimal treatment-intensity, both started their subsequent cycles of chemotherapy despite persistent PCR positivity: Patient 3 commenced fludarabine-containing chemotherapy (FLAG-Ida) and Patient 4 received interim maintenance with vincristine, dexamethasone, methotrexate and 6-mercaptopurine, uneventfully.

3.2 Changes in Ct values

The mean Ct value at diagnosis was 20.72 (18.28 - 31.15). Patient 1, with the lowest Ct value at diagnosis and on no medication tested 'negative' on repeat sampling undertaken after one month. Patient 2 continued cyclosporine without dose adjustments and tested 'negative' after 17 days. However, she re-tested 'low positive' (Ct 37.96) 42 days after the original detection of Covid-19, but without symptoms. Changes in Ct values in the two in-patients (Patients 3 and 4) are shown in Figure 1A and can be compared to the absolute lymphocyte count (ALC) at the corresponding time-points (Figure 1B). In a total of 18 measurements on both patients (12 and 6 respectively), Ct values correlated with numbers of circulating lymphocytes ($r=0.69$, $p=0.001$) and monocytes ($r=0.59$, $p=0.01$), but not neutrophils ($r=0.19$, $p=0.43$), in response to therapy.

4. Discussion

The relatively indolent infection in our patients despite recent myelosuppression and the likelihood of significant immunocompromise adds to the growing body of literature that suggests that it may be simplistic to attribute the complications of Covid-19 infections to immunosuppression associated with hematological malignancy or its therapy. [4,5] Many reports on Covid-19 complications in cancer patients have suffered with unavoidable selection bias through the inclusion of hospitalised patients and small numbers of patients with hematological cancers, with advanced age, co-morbidity, disease stage and therapies further confounding analysis and interpretation. [1] Focussed reports of Covid-19 infections in hematological malignancies [6,7] too have been confounded by age, sex or disease-stage (newly diagnosed or relapsed/refractory), often associated with frailty that pre-disposes to severe infections.

The details of our experience along with outputs from larger, recent datasets [4,5] argue against the risk of Covid-19 complications being a consequence of immunosuppression. Changes in referral patterns notwithstanding, preliminary data from the Intensive Care National Research and Audit Centre suggest that the proportion of critically ill Covid-19 infected patients with hematological malignancies or immunosuppression is lower than in a historic cohort of patients with non-Covid-19 viral pneumonia, to further support our observations. (https://www.icnarc.org/DataServices/Attachments/Download/da19fd54-70b2-ea11-9127-00505601089b). Based on the observation of correlation between longitudinal changes in Ct values and the ALC following Covid-19 diagnosis, we cautiously suggest that immunosuppression may potentially delay clearance of Covid-19, [8] but this hypothesis requires confirmation with a truly quantitative RT-PCR assay

taking into account the validity of the standard curve with reference materials or in-house plasmid controls with assigned viral copy numbers [9] before the clinical significance can be ascertained. Supporting the expert panel recommendations for disease management during the Covid-19 pandemic, [10] our report emphasizes the importance of adapting anti-cancer therapies to each patient's needs, but without undue concern about the immunosuppressive consequences of treatment.

Contributions. KB undertook collection of clinical data, BP provided and interpreted RT-PCR data and ST undertook statistical analysis and wrote the manuscript.

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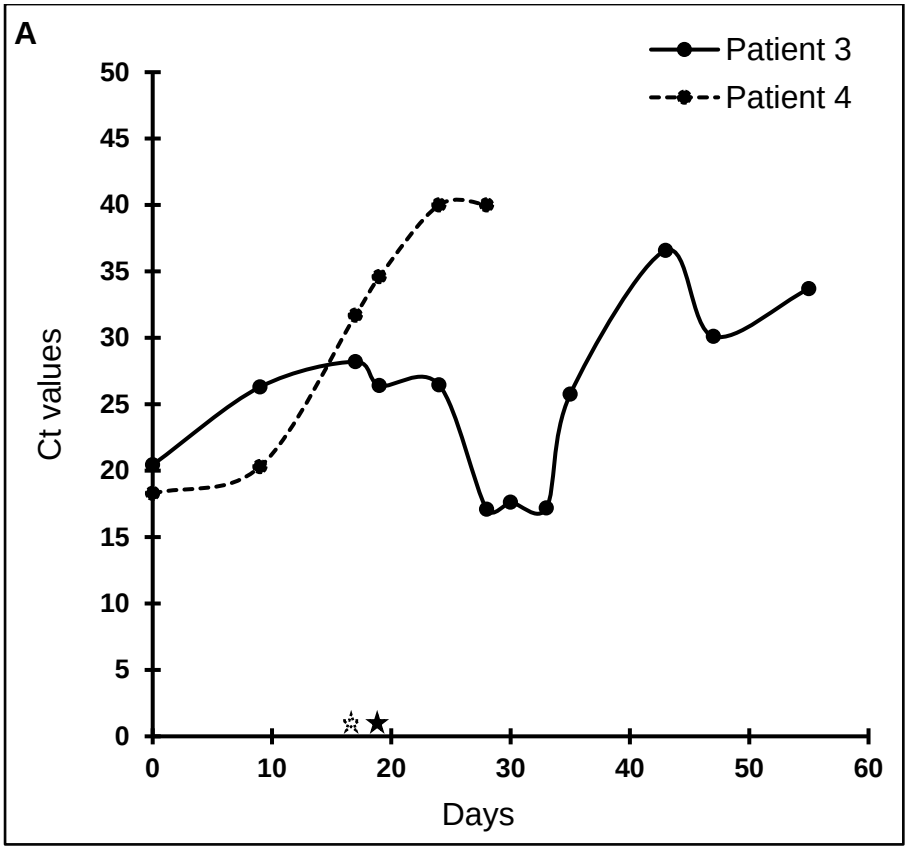
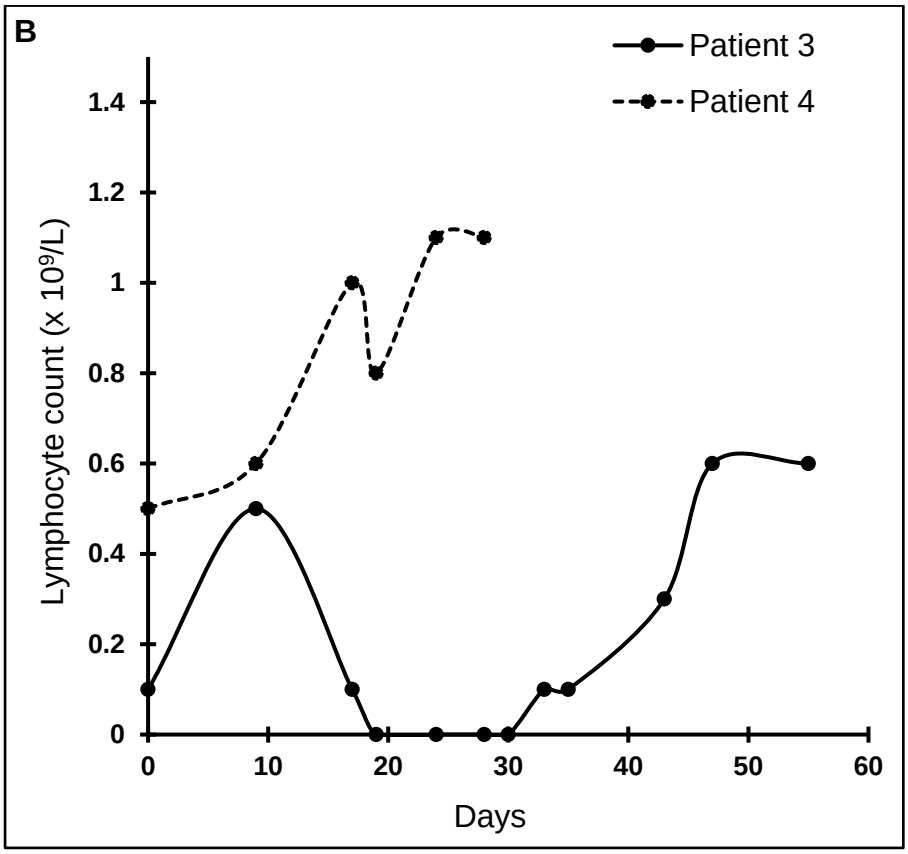
Table 1. Patient characteristics at time of detection of Covid-19.

No.	Age (years)	Sex	Co-morbidity	Diagnosis	Therapy	Duration^	ANC* x 10^9/l	ALC** x 10^9/l	Symptoms	Outcome
1	66	Male	hypertension, hyperlipidemia	acute myeloid leukemia	Vyxeos (consolidation)	25 days	1.3	1.5	fever	resolved < 24 hours
2	38	Female	obesity, trigeminal neuralgia	high-risk myelodysplastic syndrome, cutaneous graft-versus-host disease	T-deplete, unrelated donor allograft, on-going cyclosporin	15 months	3.5	1.6	cough/fever	resolved < 24 hours
3	23	Male	nil	refractory T-cell acute lymphoblastic leukemia	High-dose methotrexate and cytarabine, vincristine, dexamethasone Recent nelarabine, cyclophosphamide and etoposide	12 days	0.1	0.1	anosmia	resolved < 7 days
4	23	Male	nil	B-acute lymphoblastic leukemia	Consolidation week 8 (cyclophosphamide, cytarabine, mercaptopurine, pegylated asparaginase, vincristine)	6 days	0.4	0.5	none	remained asymptomatic

^duration from last chemotherapy, *absolute neutrophil count (range 2.0-7.5), **absolute lymphocyte count (range 1.5-4.0).

Figure 1. Longitudinal changes in Covid-19 RT-PCR Ct values and absolute lymphocyte count (ALC). Ct values from the day of diagnosis of Covid-19 infection (day 0) are shown in two patients until last follow-up (Patient 3) or a negative result (Patient 4) **(A)**, along with the day of starting further chemotherapy (☆ for Patient 3 and ★ for Patient 4). Changes in Ct correlated with the absolute lymphocyte count (ALC) measured on or within 3 days of nasal and pharyngeal swab testing **(B)** to suggest an effect of immune reconstitution/suppression on viral clearance.


A
Patient 3
Patient 4
Ct values
Days
0
5
10
15
20
25
30
35
40
45
50
0
10
20
30
40
50
60


B
Patient 3
Patient 4
Lymphocyte count (x 10⁹/L)
Days
0
0.2
0.4
0.6
0.8
1
1.2
1.4
0
10
20
30
40
50
60